Moderate and Severe Traumatic Brain Injury: Epidemiologic, Imaging and Neuropathologic Perspectives

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This article examines 3 contexts in which moderate or severe traumatic brain injury can be approached. The epidemiologic background of moderate and severe traumatic brain injury is presented, with particular attention paid to new findings from the study of a national hospital inpatient database. We review aspects of neuroimaging and how new imaging modalities can reveal fine detail about traumatic brain injury. Finally we examine the current state of neuropathologic evaluation of, and recent developments in, understanding of the neural disruptions that occur following traumatic brain injury, together with cellular reactions to these disruptions.

Brain Pathol 2004;14:185-194.

EPIDEMIOLOGY

Because traumatic brain injury often leads to disability or death, the number of brain injuries sustained each year in the United States has been the subject of intense study. As many as half of all trauma deaths in the United States involve significant injury to the brain (99). Estimates assembled from mortality and case fatality calculations on the one hand, and from studies of as few as a hundred to as many as tens of thousands of cases in various locales around the country, suggest that the incidence in the United States of persons hospitalized with any kind of brain injury (regardless of severity) is 175 to 200 per 100 000 population. Including persons with fatal brain injuries who do not make it to a hospital and persons with nonfatal brain injuries not so severe as to require hospital admission, residents of the United States may experience about 1.8 million brain injuries each year in total. One and a half million affected patients are estimated to be treated in emergency departments and released, 300 000 are estimated to be admitted to hospital and discharged alive, and 56 000 are estimated to be deaths, either at the scene of the injury or during hospitalization (56). Kraus and McArthur (55), drawing upon dozens of studies conducted nationally and internationally, calculated the average brain injury death rate at about 22 per 100 000 per year.

A number of critical methodologic concerns have slowed the search for definitive estimates of traumatic brain injury incidence and mortality. Many studies of moderate and severe traumatic brain injury, even when population-based, have been restricted in geographic scope, in time, and in numbers of included patients. Definitions of what exactly constitutes a brain injury have varied. Some fraction of persons seen in emergency rooms and admitted to hospital with one diagnosis being "brain injury" may not actually demonstrate significant neurological impairment. Many persons who sustain a traumatic brain injury either do not seek medical treatment or obtain their care from a medical practitioner in a private office and are not counted in hospital statistics. A clearer picture about traumatic brain injury might emerge if a national register of cases existed which used a uniform case definition, but no such register exists in the United States. Local, district, and state registers have been reported, and researchers have also studied entire populations of small countries. Even including the most recent large-area studies, however, calculations of the total hospitalized traumatic brain injury population vary by a factor of at least 5 and some may be difficult to extrapolate to the US experience.

While acknowledging the limitations sketched above, nationally representative estimates of hospitalized traumatic brain injuries in the United States can be calculated from an extended database collected by the Agency for Healthcare Research and Quality, an arm of the US Public Health Service. The Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample, available annually, is the largest inpatient database in the United States that includes all medical insurance payers, and allows detailed study of hospital inpatients using a uniform format (100). For the period 1998 to 2000, the database describes approximately 21.5 million discharges, regardless of health insurance status, from 994 hospitals located in about half the states of the Union, and approximates a 20% sample of all non-federal, short-term, general, and other specialty hospitals. Included as well are weights for producing national estimates. The immense size of the sample enables detailed analyses of rare conditions and specific subpopulations while guaranteeing subject anonymity.

The HCUP datasets for 1998 through 2000 were examined for the following brain injury diagnoses: fractures of the vault or base of the skull (International Classification of Diseases Codes 800 and 801) (46), other skull fractures (ICD 803), and multiple skull fractures (ICD 804), altered consciousness (ICD 780), concussion (ICD 850) and open wounds of the head (ICD 873), and for whom at least one indication was found that the individual had sustained a loss of consciousness for a period of at least one hour. That indication was drawn from the fifth digit subclassification of the ICD for selected 800 codes, which

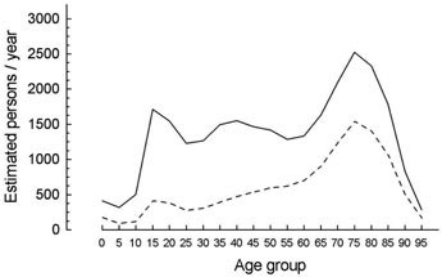

Figure 1. Estimated annual admissions for moderate or severe traumatic brain injury by age group, United States, 1998-2000. Solid line = admissions; dashed line = in-hospital deaths among those admitted. Age groups are aggregated by 5-year intervals from age 0 up to age 95; all persons older than 95 are included in the oldest age group.

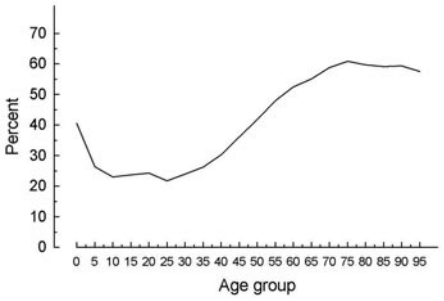

Figure 2. Percent mortality among persons admitted to hospital with moderate or severe traumatic brain injury by age group, United States, 1998-2000. Age groups are aggregated by 5-year intervals from age 0 up to age 95; all persons older than 95 are included in the oldest age group.

signifies, for those diagnoses, the duration of loss of consciousness. Hospitalized persons with traumatic brain injury and loss of consciousness of at least one hour were presumed to constitute a group with at least a moderate, if not severe, degree of injury. Once a qualifying individual was identified in the HCUP database, information was culled regarding age, sex, cause of injury, and weighting value.

The HCUP data reveal that the annual estimated incidence in the United States of moderate and severe traumatic brain injury resulting in hospitalization during 1998 to 2000 was 81 048, with an overall mortality of 43.6%. As the annual number of emergency department visits for all traumatic brain injuries has been estimated at 1 027 000 (39), the proportion of those visits that are due to moderate or severe traumatic brain injury and are admitted to hospital can be estimated as 2.63%. Using the most recent available US national statistics for deaths (2, 6), the proportion of deaths occurring in hospital among persons admitted with loss of consciousness of more than 12 hours can be estimated as 29.0% of injury-related deaths due to all causes. Because less than one person in 100 within the HCUP sample of brain-injured individuals had only a single diagnosis, and many had one or more possibly severe injuries to other parts of the body, it is important to note that this proportion includes deaths that may not have resulted from the head injury alone.

From the HCUP data, the estimated incidence of traumatic brain injury by gender shows that for every 124 males admitted to hospital, there were 100 females. Though less often admitted, women with moderate or severe brain injury were significantly more likely to die during hospitalization than males (Odds Ratio [OR] = 1.24, 95% Confidence Interval [CI] = 1.20-1.29). In contrast, some recent studies have identified males as outnumbering females among those persons identified as severely brain injured by a ratio of 3:1 (eg, 66), and deaths among adult females have been estimated at rates much lower than for adult males except over age 60, where age-specific mortality was as much as three times higher among females (eg, 27). In the HCUP dataset, females were significantly less likely than males to be diagnosed with a skull fracture (OR = 0.67, 95% CI = 0.47-0.95), a cerebral laceration or contusion (OR = 0.84, 95% CI = 0.71-0.99), or a subdural or subarachnoid hemorrhage (OR = 0.86, 95% CI = 0.75-0.98).

The estimated annual number of hospital admissions for traumatic brain injury by age group is shown in Figure 1, along with the estimated number of in-hospital deaths. Age groups were calculated in 5-year intervals (with the exception of persons older than 100 years who are aggregated together with their 95-year-old compatriots). This figure demonstrates a phenomenon repeatedly identified at coarser resolution in earlier studies: several discrete peaks exist in the age distribution. The first peak occurs in the late teenage years, while another occurs in the late 30s, and the most pronounced peak is found in the late 70s. However, unlike some reported age distributions (eg, 13, 26) in which a large number of very young persons were admitted for traumatic brain injury, the HCUP data indicate that persons under age 10 to 15 were much less likely to be admitted than any other age group except for those over age 95.

Unlike the multiple-peaked admissions distribution by age, the mortality curve for persons with moderate or severe brain injury follows a very different course: mortality was 40.6% in the very youngest age group but only 26.6% in persons ages 5 to 10, declining to 21.8% in persons ages 25 to 30 (Figure 2). However, above age 30, mortality appeared to steadily increase up to ages 75 to 80 (60.9%). For persons over age 80, in-hospital mortality is estimated at 59.5%. These findings contrast with other recent studies of the relation of age to mortality in severe traumatic brain injury. For example, Gómez et al (36) reported a significant linear trend in mortality, rising from 41.3% among persons aged 15 to 25, to 86.8% among persons older than 65, using a 10-year sample of admissions in Spain. Hukkelhoven et al (45) found a strong linear trend in mortality by age using data from 5662 patients assembled from a variety of sources. Neither study, however, included pediatric cases or was able to differentiate among persons older than 65. The HCUP data show a strongly linear component to the relationship between age and mortality only for persons between ages 25 and 75 years.

Motor vehicle accidents (MVAs) are the most frequent cause of traumatic brain injury in the HCUP datasets. The causes of injury are available for most patients in the sample and are denoted by ICD codes beginning with the letter E. MVAs (codes E810 through E825) were identified as the cause of injury for 36.2% of the individuals in the sample. Falls (codes E880 through E888) were found for 20.1%. Suicides and self-inflicted injuries (codes E950 through E959) were identified for 9.4%. Assaults, homicides and other injuries purposefully inflicted by other parties (codes E960 through E969) were found for 7.4%. Child abuse (code E967) was found in 3.6%. Of note, MVAs were 4 times more frequent than falls as a cause of injury from the youngest ages through ages 45 to 49. However, falls were 3 times more frequent than MVAs above age 50. The mix of causes of traumatic brain injury appears to vary across cultures; in a recent Swedish study (5) for example, traffic accidents were less than half as frequent and falls were more than twice as frequent as the causes identified in the HCUP data.

Limitations of the HCUP datasets include a reliance on voluntary participation by statewide data collection activities undertaken by state data organizations, hospital associations, and other private organizations. This may mean that both data coding and completeness could be influenced by outside factors such as financing for data collection activities. The fact that the ICD diagnostic codes do not completely describe all possible intracranial traumas is also important to note. Additional limitations of the HCUP dataset are that persons cannot be identified as to whether they failed to regain consciousness while hospitalized, neurological status at discharge cannot be determined among those discharged alive, and no data are available concerning outcomes after discharge. The HCUP dataset does not provide information on prevalence. Prevalence measures all persons at a specific point in time who have the condition of interest and includes persons newly diagnosed as well as those with residual disability or impairment. Few published prevalence estimates are available for brain-injured persons; Recent estimates show that overall prevalence in the United States was 2%, or 5.3 million persons living with a traumatic brain injury-related disability (107).

Catastrophic brain injury followed by failure to regain consciousness, persistent vegetative state (PVS), was first identified before the 20th century, though not named as such until the inclusion of that descriptive phrase in the Glasgow Outcome Scale (51). The fundamental basis for the diagnosis of PVS is wakefulness without awareness. Eyes can be roving and may appear to track moving objects. Orienting responses may be present to light, sound or movement. Limbs are usually spastic, with grasping reflexes and other signs such as gag reflex, teeth-grinding, and emitting of sounds, which may be misinterpreted as intentional.

The epidemiology of PVS is not well-documented. An analysis of 1203 cases with severe posttraumatic coma in Milan a quarter-century ago reported that 5.1% developed a complete apallic syndrome, denoted by alertness without awareness, mass movements only, primitive motor responses, and other disruptions (82). Sixty-one percent of these patients succumbed within weeks or months, while 5% survived without changes for up to 5 years. Among the survivors, 16% showed severe neurological or neuropsychological disabilities, 6% recovered with some neurological sequelae, and 8% recovered sufficiently to return to work. Mortality was directly related to age: 33% in those under 14 years, but 77% in those over age 30. A contemporary Japanese study identified 110 individuals in PVS, 35% of whom the cause of brain damage was a traumatic head injury (41). One-year mortality in this subset was 26.3%; the 2-year cumulative mortality was 42.1%; and the 3-year cumulative mortality was 55.3%. Recovery at 3 years was limited: among all the survivors at 3 years, only one had regained both conversation and unassisted mobility, while 16% showed slight improvement, 52% were unchanged, and 29% had deteriorated slightly compared to the preceding assessment. Prevalence was estimated to be 2.5 per 100 000 population. Of 434 persons in a vegetative state one month following injury, 33% recovered consciousness by 3 months, 46% by 6 months, and 52% by 12 months (44, 73), figures very similar to those obtained in study of the Traumatic Coma Data Bank (59). After 12 months, the proportion with recovery of consciousness was exceedingly small (1.6%). Among those persons who awoke and progressed to good recovery by 12 months (0.5%), over half were already showing signs of improvement at 3 months.

NEUROIMAGING

Imaging has been shown to play an important role in the evaluation of patients with traumatic brain injury. Traditional imaging sequences—CT (eg, 31), MRI, SPECT, PET, and MR spectroscopy (eg, 20), and more recently, new pulse sequences employing echo planar technology, are revolutionizing our understanding of brain injury. Imaging findings have been shown to correlate strongly with both clinical and neurobehavioral outcome measures (8).

Traditional spin-echo (SE), and new gradient echo (GRE) and echo-planar (EPI) pulse sequences have increased the sensitivity of MR to a variety of brain pathologies frequently seen in those with traumatic brain injuries. These sequences include fluid attenuated inversion recovery sequences (FLAIR), 2-dimensional gradient-echo spoiled fast low-angle single-shot (2D-FLASH) sequences, diffusion weighted echo-planar sequences (EPI-DWI), and volumetric sequences such as the 3-dimensional spoiled gradient recalled (3D-SPGR) and multi-planar magnetization prepared rapid gradient echo (MP-RAGE) sequences. When used in combination and coupled with the anatomic findings, the specific pattern of signal intensities present in sequences employing these MR imaging protocols can be used to infer the tissue state and likely mechanism of injury. The diffusion-weighted sequence (DWI) is exquisitely sensitive to tissue ischemia and tissue infarction.

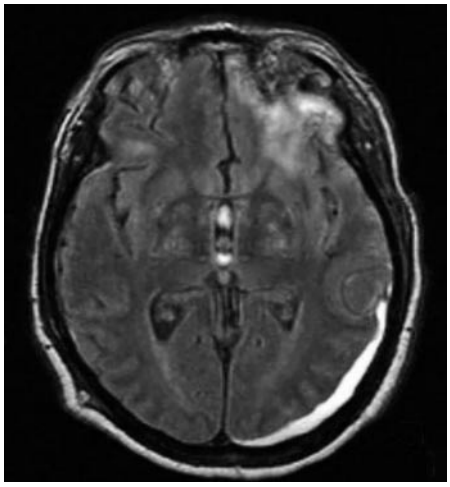

Figure 3. Illustrative axial FLAIR sequence in a patient with subdural hematoma. Note crescentic hyperintense collection of blood along the left posterior parietal subdural space.

The 4 most common types of brain injury are subdural and epidural hematomas, brain contusions with or without hemorrhagic transformation, diffuse axonal injury and anoxic/hypoxic or hypotensive brain injury. Each of these types of brain injury has a specific imaging pattern.

For instance, subdural hematomas are visible as curvilinear, extraaxial collections of fluid with high T1W and high or low T2W signal intensity that do not respect calvarial sutural demarcations and are associated with mass effect upon the underlying brain (Figure 3). Epidural hematomas can be distinguished as lenticular-shaped collections of extraaxial fluid over the cerebral surface. These collections are bounded by the calvarial sutures and are very frequently associated with skull fractures. Progressive "blossoming" of hemorrhagic injuries is a problem for up to half of traumatic brain injured patients (76), and requires careful repeated scanning.

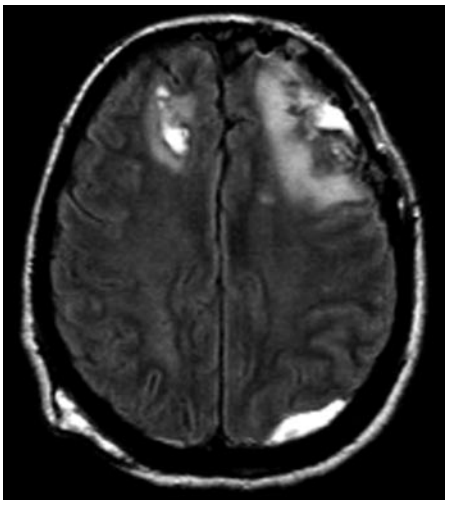

Figure 4. Illustrative axial FLAIR sequence in a patient with contusion demonstrates an irregular area of hyperintense signal involving the left anterior frontal lobe indicating tissue edema from brain contusion. Note peripheral region of low signal intensity within contused tissue indicating region of hemorrhagic transformation.

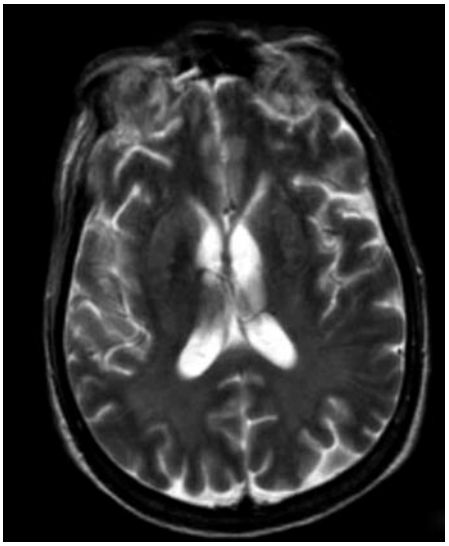

Figure 6. Illustrative axial T2-weighted FSE sequence in a patient with anoxic/hypoxic brain injury demonstrates reversal of the normal grey-white matter signal intensity relationship. Note cortical ribbon is hypointense relative to cerebral white matter, indicating the presence of diffuse anoxic/hypoxic cortical injury.

At the initial time of injury, regions of brain contusion can be identified and quantified based on a region of low T1W and high T2W and FLAIR signal intensity with associated mass effect, indicating tissue swelling (106). Areas of hemorrhagic transformation within the contused brain appear as well-circumscribed regions of very low signal intensity on the 2D-FLASH sequences, with corresponding high or iso-signal intensity relative to brain in the same region on the T1W sequence (Figure 4).

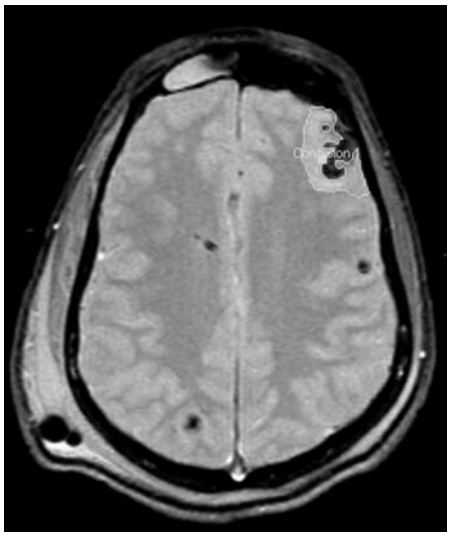

Figure 5. Illustrative axial gradient echo (T2*/2D-FLASH) image in a patient with diffuse axonal injury. Note the presence of three small rounded markedly hypointense foci of blood degradation products within the cerebrum indicating the presence of scattered shear foci.

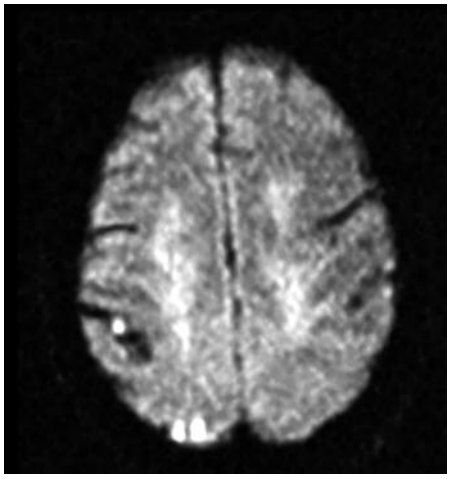

Figure 7. Illustrative axial diffusion-weighted image (b = 1000T) in a patient with anoxic/hypoxic brain injury demonstrates several small rounded foci of hyperintensity in the right parietal convexity. The foci demonstrated matching areas of high T2-weighted and FLAIR signal intensity. The signal pattern is compatible with subacute ischemia within sites of cerebral contusion.

Diffuse axonal injury can be identified on the 2D-FLASH sequences as small, punctate, single or distributed foci of very low signal intensity in typical locations, including the gray-white matter junction of the cerebrum, the pericallosal regions, and the brainstem (60). These foci are generally invisible on all other sequences. The sensitivity of 2D FLASH sequences for small shear injury is suspected to be higher than for CT. However, CT has also been described as revealing small hyperdense foci compatible with shear injury in the parasagittal and subcortical regions of the cerebrum. When routine CT scans do not show small shear foci, histopathologic examination of the brain can be used to identify shear injury. The appropriate MR sequences would clearly show evidence of cerebral diffuse axonal injury as exemplified in Figure 5. In a study of postmortem brain tissue, 41% of those who had a non-missile traumatic brain injury exhibited axonal injuries (74).

Hypotensive brain injury typically causes ischemia and infarction in watershed zones between the major intracranial vascular arterial territories. These regions of brain injury appear hyperintense in the DWI sequence in the hyperacute period, and after 6 to 12 days post insult, also show corresponding T2W and FLAIR sequence hyperintensity, probably reflecting progression to tissue death (63).

Anoxic/hypoxic brain injury can be identified by a characteristic inversion of gray-white matter signal intensities on the T2W and FLAIR sequences (Figure 6), with the gray matter appearing lower in signal intensity compared to the white matter, when normally the reverse relationship is true, and by the appearance of high DWI signal intensity in those regions in many cases (Figure 7). In addition, high T2W, FLAIR and DWI signal intensities are commonly present in portions of the basal ganglia. Finally, in the acute or delayed setting, brain death can be inferred when there is loss of normal gray-white matter differentiation, diffuse cerebral edema as defined by effaced sulci and compressed ventricles, and evidence of transtentorial, uncal or subfalcial herniation. Anoxia and hypoxia have been described in the setting of traumatic brain injury, generally resulting from respiratory arrest or compromise of oxygen exchange as may occur with neurogenic pulmonary edema (65).

MR can be used to identify the consequences of acute brain injury in the delayed setting. For instance, MP-RAGE sequences can be used to measure the volume of lost tissue when hemorrhagic contusions transform into encephalomalacic cavities as a result of liquefactive necrosis and subsequent phagocytic activity. These regions appear as areas of profound T1W signal hypointensity, generally with sharply defined margins (Figure 8). FLAIR sequences can be used in a delayed scan to determine the volume of

tissue gliosis, or scarring, occurring in the brain parenchyma surrounding encephalomalacic cavities resulting from non-fatal tissue damage (Figure 9). Volumetric MR sequences can also be used to measure intra-individual changes in the volume of whole brain regions or specific brain structures following traumatic brain injury. Even the distal consequences of local injury can be estimated using T1W or volumetric and T2W or FLAIR sequences, which may show regions of regional volume loss including Wallerian degeneration, or tract-specific tissue gliosis. Cerebral MRI findings, particularly the imaging of lesions in the corpus callosum and dorsolateral brainstem, have been shown to be predictive of outcome in individuals with PVS (52).

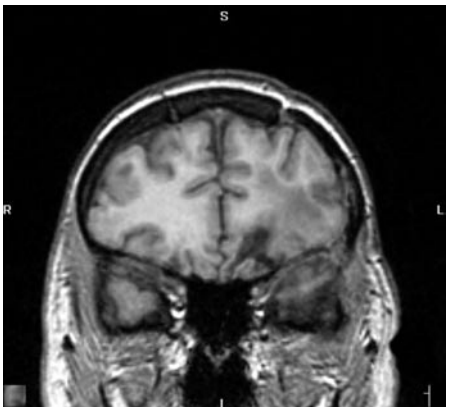

Figure 8. Illustrative coronal 3D-SPGR volumetric acquisition in a patient with volume loss following brain injury demonstrates irregular region of T1 hypointensity in the inferior aspect of left frontal lobe, indicating the presence of encephalomalacia resulting from a hemorrhagic contusion at this location.

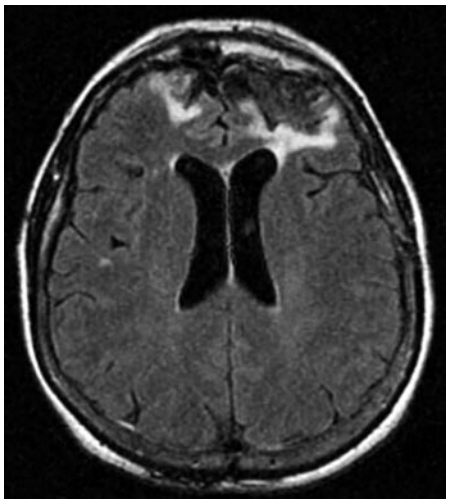

Figure 9. Illustrative axial FLAIR sequence in a patient with volume loss following brain injury demonstrates the encephalomalacic cavity of the left frontal lobe shown in the preceding figure. Note surrounding rim of hyperintense signal indicative of tissue gliosis.

NEUROPATHOLOGY

The neuropathology of traumatic brain injury (TBI) encompasses complex gross, microscopic, biochemical and genetic alterations to the central nervous system and its coverings (25, 30, 35, 37, 54, 62, 72, 79-81). Traumatic brain injury produces both focal and diffuse insults. The mechanisms of injury include impact, rotational/inertial effects or both impact with rotation; the end result depends upon the amount of energy transferred to the head, the site of impact and duration of injury (7, 37, 48, 80, 110, 113). Investigators have used different experimental animal models (eg, cortical impact, fluid percussion, impact acceleration) as well as human tissue to study the temporal and morphological differences between irreversible and reversible damage. Furthermore, cDNA microarray and proteomic technologies are starting to be used to help understand the pathogenesis of TBI (24, 34, 64, 68, 92, 94, 112). This research has implications for both treatment and prognosis of TBI as well as for forensic pathology, eg, improved estimation of the cause and timing of injury.

In forensic pathology, careful examination of the scalp in cases of blunt force injuries may provide valuable information useful in the interpretation of intracranial injuries. Impact sites are usually identifiable, but in some cases this may require careful inspection, shaving of the hair to reveal faint patterns of contusion, abrasion or lacerations, and attention to size and location of subgaleal contusions. In the event of a motorcycle accident, since a rider's helmet frequently obscures recognizable scalp trauma, inspection of the helmet may yield clues as to the site and severity of impact. A working knowledge of the scene and circumstances that surround the incident should be the expectation of the investigating pathologist. Attention to these details, although a time investment up front, yields dividends when the investigator is asked to interpret head injuries in light of conclusions drawn from animal models or before a jury.

Intracranial extra-axial hemorrhages consist of epidural hematomas (EDH), subdural hematomas (SDH) and subarachnoid hemorrhages (SAH). Epidural hematomas, the result of impact injuries, typically accompany a skull fracture and laceration of a meningeal artery. These can produce a mass effect with displacement of the dura mater broadly over the surface of compressed sulci and gyri. In contrast, in SDH blood insinuates itself between gyri and down sulci (38). Although capable of resulting in mass effect, SDH does not compress sulci because the hydrostatic pressure is the same over and between gyri. Subdural hematomas are usually the result of torn bridging veins following acceleration/deceleration injury, less often due to a ruptured cerebral lobe or laceration of a cerebral artery. They are often associated with other parenchymal injuries that contribute to a worse prognosis (105). Traumatic subarachnoid hemorrhage is frequently found following TBI; it is unusual to have this as the sole finding in severe cases, and it also appears to imply a worse prognosis (47, 67). Fatal traumatic basilar SAH may be the result of neck injury, in some cases due to damage to the vertebral artery; these seem to be more common in inebriated young males (10, 22).

Focal non-penetrating blunt force injury of the brain parenchyma usually means a cerebral or cerebellar contusion, less often a laceration. Contusions may or may not be associated with skull fractures. They are found on the crests of gyri, giving the gray matter a punctate or confluent hemorrhagic appearance (Figure 10A). Under the microscope shows that small hemorrhages appear as streaks oriented perpendicular to the surface. More extensive hemorrhages may involve the underlying cortico-white matter junction or, less frequently, may extend into the underlying white matter (eg, in a coagulopathic state). Cortical contusions may be differentiated from hemorrhagic infarcts by the destruction of the molecular layer as a result of the trauma. After a period of weeks to years, the contusions take on an orange-light brown discoloration due to hemosiderin deposition associated with irregularity of the cortical surface. Long-term sequelae can result in Wallerian degeneration of corticospinal tracts (Figure 10B). Contusions have been accorded descriptive labels: coup contusions, beneath the impact site on the head; contre-coup, away from the impact site; intermediate contusions, somewhere in between; fracture contusions, associated with a skull fracture overlying the contusion; gliding contusions, although a diffuse type of

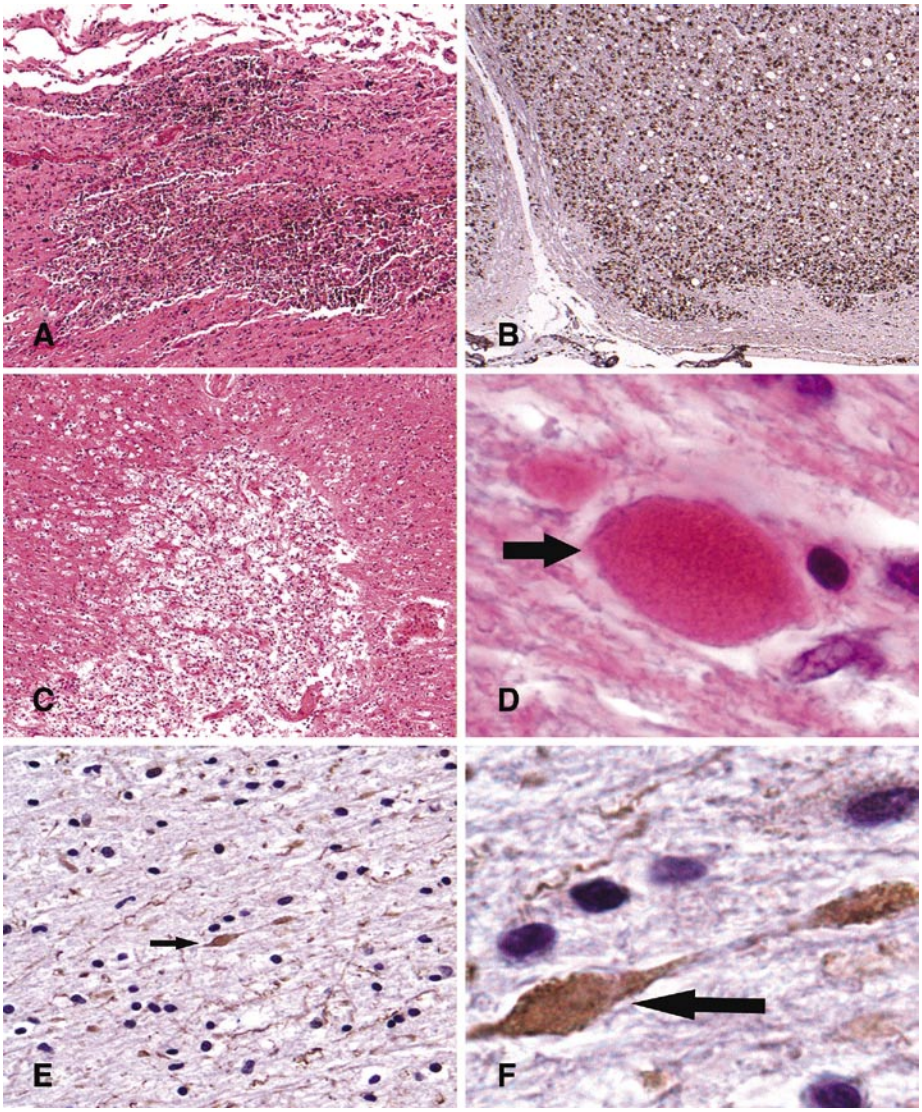

Figure 10. A. Cortical contusion in the right frontal lobe with destruction of superficial cortical layers, hemosiderin-laden and foamy macrophage infiltration in a 30 year-old male motorcyclist who sustained severe closed head injury 5 months prior to death. H&E ×31. **B.** Medullary pyramids with Wallerian degeneration and intense macrophage activity, (same case as above) 5 months post-injury. Immunohistochemistry for CD68 ×31. **C.** Dorsal corpus callosum with diffuse axonal injury, Grade II, (same case as above) 5 months post-injury. H&E ×63. **D.** Balloon-like swelling within corpus callosum (same case as above). H&E ×1725. **E.** Axonal balloon (neuroaxonal spheroid) within cortical white matter (same case as above), 5 months post-injury. Immunohistochemistry for neurofilament ×350. **F.** Neuroaxonal spheroid .Immunohistochemistry for neurofilament ×1725.

TBI, are small linear cerebral white matter hemorrhages in a parasagittal distribution. The classical contre-coup contusion occurs when the head is in motion and strikes an unyielding object, eg, a fall onto the occiput producing contusion on the gyri recti of the frontal lobe, the temporal or frontal poles. Occasionally these are found with fractures of the thin bony orbital or cribiform plates. Interestingly, the opposite situation, a fall upon the frons, almost never produces a contusion on the posterior aspect of the brain. Severe head injury can produce both focal contusions and lacerations of the brain; typically, a laceration of the brain implies more absorbed energy, such as is found in a penetrating gunshot wound, depressed and comminuted skull fractures, or, if located in the brainstem, subluxation of the atlanto-occipital joint, or basal skull fracture, eg, a hinge-type fracture.

Diffuse brain injury involves either diffuse axonal injury (DAI), diffuse vascular injury (DVI), ischemic brain injury or diffuse brain swelling (10, 37, 88). DAI is the product of inertial forces from acceleration/deceleration of the brain resulting in pressure gradients and mechanical strains, both shear/tensile and compressive (30, 37, 88). Whether an impact is always associated with diffuse injury in child/infant abuse cases is controversial (4, 23); according to Ommaya et al, impact and impulsive loading differ in application and consequences and, therefore, the two terms should not be combined into one name, such as "shaken baby syndrome" unless both are known to have happened concurrently (80). Under some circumstances such as motor vehicle fatalities, one frequently finds a mixture of focal and diffuse injury.

The severity of DAI can vary from mild to severe and correlates with a patient's prognosis. One scheme classifies DAI into three grades: Grade I, axonal damage in the white matter without focal lesions in the corpus callosum; Grade II, widespread axonal damage with focal lesions in the corpus callosum but not the brainstem (Figures 10C, D); Grade III, axonal damage in the white matter, with focal lesions in the corpus callosum and the brainstem (1). On gross examination, punctate or streak-like white matter hemorrhages and/or tiny lacerations may be found in the para-sagittal white matter, the corpus callosum or brainstem. It is now recognized from work in animal models of TBI, that some—probably most—of the axonal damage noted on light microscopy is a consequence of complicated pathologic processes begun with the initial trauma, that proceed to ultrastructural changes and interruption of axonal transport and may later culminate in axonal transection and formation of neuroaxonal spheroids (49, 50, 69, 84). The initial insult appears to cause transient alteration of the integrity of the axonal membrane, associated with changes in ionic (calcium, sodium, potassium) concentrations, axonal transport disruption, excitotoxic transmitter effect, free radical formation and lipid peroxidation (28, 70, 84, 89). The axonal damage ultrastructurally correlates with local decreased density of microtubules, compaction of neurofilaments with loss of neurofilament side arms, and mitochondrial injury (78, 84, 102). Disturbance of fast anterograde axonal transport can be demonstrated within 30 minutes of impact in an animal model (101, 102) and within one to 2 hours in humans (71, 109), by immunohistochemical staining for amyloid precursor protein (APP) or by demonstrating ultrastructural

accumulation of intra-axonal vesicles that contain APP (11, 32, 33, 40, 57, 75, 101-103). Amyloid precursor protein is a transmembrane glycoprotein made in the perikarya of neurons and transported down the axon attached to vesicle membranes. Of note, according to Stone et al, antibody against the C-terminal end of APP produces less background immunopositivity than antibody against the N-terminus (101). Intra-axonal APP immunoreactivity is not specific for DAI, being also found in brains with hypoxic/ischemic injury, infarction, abscess and multiple sclerosis (53, 75), but is nevertheless a useful immunohistochemical marker for this phenomenon.

Use of animal models of TBI has revealed temporal-spatial relationships between ultrastructural and light microscopic findings. Pettus and Povlishock, using a fluid percussion injury cat model, demonstrated that axonal cytoskeletal collapse of interneurofilament spacing occurs within five minutes (84). In a rat impact acceleration model of TBI, Stone et al demonstrated APP immunoreactive axonal accumulation within 30 to 60 minutes following trauma (103). The APP immunoreactive swellings correspond to nodal and paranodal accumulations of organelles and vesicular structures that immunohistochemically stain for APP on electron microscopic images within otherwise intact axons. Also noted within one hour after trauma were larger disconnected axons with accumulations of organelles that appear to cap central areas composed of compacted neurofilaments. Subsequently, Stone et al have demonstrated that neurofibrillary compaction can occur in rat axons independent of demonstrable impairment of axonal transport. Ultrastructurally, these thinner neurofilament immunoreactive axons show compacted neurofilaments with shortening of sidearms and dilatation of mitochondria. Whether there are 2 types of traumatically injured axons, ie, one that is immunoreactive for APP and another that is only immunoreactive for NF, is currently unknown. Additional immunohistochemical markers that have been used for demonstration of axonal swellings include neurofilament ubiquitin and Aβ, a peptide breakdown product of APP important in the pathogenesis of Alzheimer disease (40, 98) (Figure 10E, F).

Biochemical changes in the brain produced by trauma result in increased intracellular calcium, glutamate release and toxicity, activation of neuronal glutamate receptors, activation of neutral proteases, increased nitric oxide production, free radical generation, including peroxynitrite free radicals, superoxide and hydrogen peroxide, with subsequent membrane, nuclear and mitochondrial damage (12, 14, 21, 43, 58, 61, 62, 85, 93). This may be followed by cytochrome c oxidase release, activation of caspases and apoptosis. Neuronal nitric oxide synthase activation with free radical generation and DNA damage also precedes poly (ADP-ribose) polymerase (PARP) activation. Activation of this enzyme may result in depletion of cellular NAD, reduction of ATP stores, energy failure and cell necrosis. Hortobagyi et al (43) used a rat brain cryogenic injury model, to demonstrate that selective inhibition of PARP or nNOS resulted in neuroprotection and decreased poly(ADP-ribose) concentration, the end-product of PARP, in the injured cortex. Nitric oxide also appears to affect cerebral blood flow in TBI, possibly through its production by endothelial derived nitric oxide synthase and/or production by inducible nitric oxide synthase in white blood cells. Hlatky et al used a microdialysis probe inserted into brains of traumatized patients from which dialysate was sampled for levels of nitrate and nitrites, the end products of nitrous oxide. Their results showed a correlation between nitric oxide levels and changes in regional cerebral blood flow immediately after injury that the authors attributed to endothelial nitric oxide synthase activation (42).

The presence of mitochondrial perturbation in traumatic axonal damage has also been supported by immunohistochemical and ultrastructural studies in a rodent impact acceleration model. Based upon work by Buki et al, it appears that early changes (up to 15 minutes following trauma) in axonal damage are the consequence of a calcium-provoked cascade of enzymatic activity beginning with calpain-mediated activation. These are followed by mitochondrial perturbation associated with cytochrome c release and caspase induction, from 60 to 360 minutes later (12). Possible therapeutic targets, therefore, include calcium activated neutral proteases and the mitochondrial permeability transition (MPT) pore. Studies that use cyclosporin A have shown a reduction in TBI in animal models, possibly through such a mechanism. Cyclosporin A is known to protect against mitochondrial failure, possibly through the MPT, as well as against calcineurin, a calcium activated phosphatase, and it has been shown to result in reduced contusion volume in focal contusion animal models (3, 77, 97, 104). According to Okonkwo et al, this drug was shown to be effective when administered intravenously as well as intrathecally in a rodent impact acceleration model (77) .

Other recent findings with possible prognostic and therapeutic potential include the observations that activated CD 4 T-cells may exacerbate acute damage in TBI (29), interleukin 6 may have neuroprotective properties in TBI (111), and metallothionein-IIA may promote neurite elongation and wound healing(19). Sex hormones, like progesterone, can reduce cerebral edema and secondary neuronal degeneration (95, 96). Selective blockage of endothelin-1, a potent vasoconstricting peptide, in closed head injury appears to improve survival in a rat model (83, 114). When glutamate activates NMDA receptors local cerebral vascular dilatation occurs, perhaps in response to local increased metabolic demands. However, in a piglet fluid percussion injury model there was a decrease in the compensatory NMDA vasodilatation. One pathway that contributes to this alteration appears to involve protein kinase C activation, protein tyrosine kinase (PTK) activation and mitogen activated protein kinase (MAPK) activation demonstrated by the use of chemical inhibitors of PTK and MAPK (85). In addition to the tissue studies of TBI, mention should be made of potential surrogate markers of brain cell injury such as serum levels S100B (91), and prognostic markers such as cerebrospinal fluid levels of free fatty acids, non-specific esterase and F2-isoprostane are currently being investigated (86, 87, 108).

Regeneration following TBI offers hope of repair, improved prognosis and potential for therapeutic augmentation. That adult mammalian brains produce stem and progenitor cells and, in addition, that stem cells from outside the central nervous system can transform into neural type cells, encourages such hope (9, 15, 16). In an animal study of controlled cortical impact, nestin-immunoreactive cells were found near the injury site (17). Nestin is an intermediate filament found in immature cells. The observation

of increased staining for this molecule in traumatized brains may reflect a compensatory injury-induced repair mechanism. Interestingly, the same study demonstrated a transient increase in NG-2 immunoreactive oligodendroglial precursor cells that may affect repair via remyelination or by influencing synaptic plasticity. In a fluid percussion rat injury model a persistent increase of subventricular proliferating cells (Ki67 and proliferating cell nuclear antigen immunoreactive) was also found after a one-year follow-up (18). This may also be a reflection of a repair mechanism, although it should be noted that the affected brains demonstrated marked neuronal loss and ventriculomegaly.

Finally, brief mention must be made of attempts to understand the pathogenesis of TBI through gene microarrays. Several studies have recently reported changes in up- and down-regulation of hundreds of genes following TBI (64, 68, 92, 94, 112). Interpretation of these data is difficult since the genes identified are involved in multiple cell processes, while many of those identified correspond only to expressed sequence tags with no known function. In addition, genes previously not thought to be associated with TBI have been noted to have increased expression. Some changes in gene expression levels support evidence derived from other investigative techniques. For example, in a study by Price et al, up-regulation of calcineurin was found following hippocampal perforant pathway injury (90). Calcineurin activity appears to affect growth cones and synapses, and may restrict neurite outgrowth, important events in neuronal repair. Manipulation of this enzyme's activity, eg, by cyclosporin A, or the products of other upregulated genes, and/or replacement of those products reduced by gene down-regulation may provide further therapeutic targets.

ACKNOWLEDGMENTS

This work was supported by NIH Grant NS 30308.

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